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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/14, A61L 15/44	A1	(11) International Publication Number: WO 96/37231 (43) International Publication Date: 28 November 1996 (28.11.96)
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(21) International Application Number: PCT/US96/06868
(22) International Filing Date: 13 May 1996 (13.05.96)

(30) Priority Data:
08/452,468 26 May 1995 (26.05.95) US

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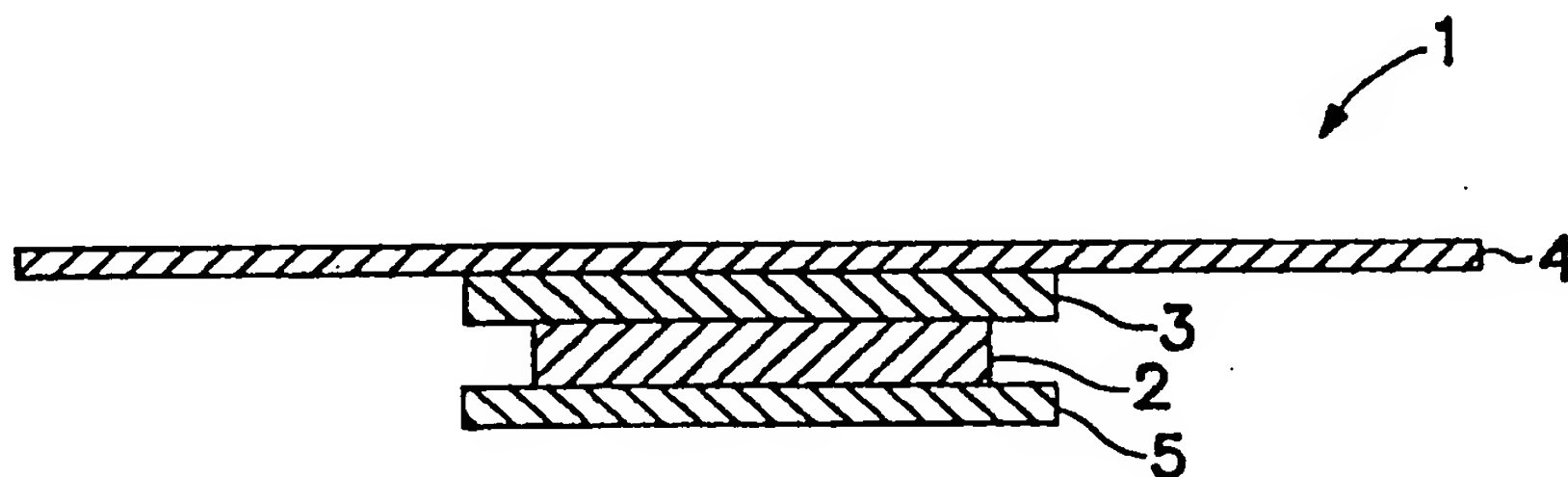
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(81) Designated States: AU, CA, CN, JP, KR, MX, NZ, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SKIN PERMEATION ENHANCER COMPOSITIONS USING ACYL LACTYLATES



(57) Abstract

The present invention is directed to the transdermal administration of a drug together with a suitable amount of an acyl lactylate permeation enhancer. The invention includes a transdermal drug delivery device comprising a matrix adapted to be placed in drug-and permeation enhancer-transmitting relation with a skin site. The matrix contains sufficient amounts of an acyl lactylate permeation enhancer and drug, in combination, to continuously administer drug to the systemic circulation of a patient at a therapeutically effective rate. The invention is also directed to compositions and methods for transdermal administration of a drug together with an acyl lactylate permeation enhancer, alone or in combination with other enhancers.

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1 **SKIN PERMEATION ENHANCER COMPOSITIONS**
2 **USING ACYL LACTYLATES**

3
4 **FIELD OF THE INVENTION**

5
6 This invention relates to the transdermal delivery of drugs or other
7 biologically active agents and more particularly to methods and compositions
8 for enhancing the percutaneous absorption of drugs or other agents when
9 incorporated in transdermal drug delivery systems or devices. Particularly,
10 this invention relates to the use of acyl lactylates as permeation enhancers for
11 transdermal systems or compositions.

12
13 **DESCRIPTION OF TERMS**

14
15 As used herein, the term "transdermal" delivery or administration refers
16 to the delivery or administration of agents by permeation through a body
17 surface or membrane, preferably intact skin, by topical administration.

18 As used herein, the term "therapeutically effective" amount or rate
19 refers to the amount or rate of drug or active agent needed to effect the
20 desired therapeutic result.

21 As used herein, the phrase "sustained time period" intends at least
22 about 12 hours and will typically intend a period in the range of about one to
23 about seven days.

24 As used herein, the phrase "predetermined area of skin" intends a
25 defined area of intact unbroken skin or mucosal tissue. That area will usually
26 be in the range of about 5 cm² to about 100 cm².

1 As used herein, the expressions "drug" and "agent" are used
2 interchangeably and are intended to have their broadest interpretation as to
3 any therapeutically active substance which is delivered to a living organism to
4 produce a desired, usually beneficial, effect.

5

6

BACKGROUND OF THE INVENTION

7

8 Acyl lactylates are represented by the general structure:
9 $R-CO-(OCH_2CH_3CO)_n-OH$ where R is a straight or branched alkyl or aryl
10 group consisting of 3 to 20 carbons and $n = 1$ to 10. Acyl lactylates have
11 been used in the food industry as dough conditioners and softeners and as
12 oil-in-water emulsifiers in nondairy compositions such as coffee whiteners and
13 vegetable oil based whipped toppings. They have also been used as
14 emulsifiers in analgesic stick compositions and in conjunction with other
15 co-emulsifiers to produce an emulsion base for cosmetic or pharmaceutical
16 compositions. Typically, acyl lactylates are commercially available as a salt
17 form for use in cosmetic formulations. The salt form is not effective as a
18 permeation enhancer.

19 Other uses of acyl lactylates include their use as antimicrobial or
20 antibacterial agents, and as a protectant against hair loss or in topical
21 compositions for inducing, maintaining, or increasing hair growth. In general,
22 permeation enhancers that are not normally toxic at the concentrations
23 employed in cosmetic or medical compositions may exhibit toxic effects at the
24 higher concentrations required to produce adequate permeation
25 enhancement. Accordingly, acyl lactylates have not been used as a
26 permeation enhancer alone or in combination with other permeation
27 enhancing agents in order to increase the permeability of a body surface or
28 membrane to a drug or active agent to transdermally deliver the drug or agent
29 to the systemic circulation of a patient.

1 US Patent No. 4,184,978, incorporated herein in its entirety by
2 reference, describes stable oil-in-water emulsion systems for use in
3 cosmetics, toiletries, and pharmaceuticals. Acyl lactylates are disclosed as
4 suitable emulsifiers.

5 US Patent No. 4,301,820, incorporated herein in its entirety by
6 reference, describes a composition comprising at least one fatty acid lactylate
7 and/or glycolate as a humectant compound in permanent waving
8 compositions.

9 U.S. Patent No. 4,702,916, incorporated herein in its entirety by
10 reference, describes the use of acyl lactylates as emulsifiers in analgesic gel
11 stick compositions.

12 U.S. Patent No. 5,124,354, incorporated herein in its entirety by
13 reference, describes a special protein tyrosine kinase inhibitor and a
14 cosmetically acceptable vehicle. Surface active agents, including acyl
15 lactylates, are disclosed as penetration enhancers that improve delivery of the
16 composition to its site of action in the immediate environment of the hair
17 follicle close to the dermal papilla.

18 European Patent Application 0 573 253 incorporated herein in its
19 entirety by reference describes an anti-bacterial cosmetic composition for
20 topical application to the skin and/or hair comprising C₆-C₁₂ acyl lactylate or a
21 derivative thereof as an anti-bacterial substance. The composition is
22 especially beneficial in the treatment of unwanted hair loss.

23 European Patent Application 0 572 271 incorporated herein in its
24 entirety by reference describes the use of acyl lactylates as preservatives in
25 topical cosmetic compositions for prevention of the growth of undesired
26 microorganisms in the skin or hair.

27 The transdermal route of parenteral delivery of drugs provides many
28 advantages, and transdermal systems for delivering a wide variety of drugs or
29 other beneficial agents are described in U.S. Pat. Nos. 3,598,122; 3,598,123;
30 3,731,683; 3,797,494; 4,286,592; 4,314,557; 4,379,454; 4,435,180;

1 4,559,222; 4,568,343; 4,573,999; 4,588,580; 4,645,502; 4,704,282;
2 4,816,258; 4,849,226; 4,908,027; 4,943,435; and 5,004,610, for example,
3 all of which are incorporated herein by reference. In many cases, drugs
4 which would appear to be ideal candidates for transdermal delivery are found
5 to have such low permeability through intact skin that they cannot be
6 delivered in therapeutically effective amounts from reasonably sized devices.

7 In an effort to increase skin permeability so that drugs can be delivered
8 in therapeutically effective amounts, it has been proposed to pretreat the skin
9 with various chemicals or to concurrently deliver the drug in the presence of a
10 permeation enhancer. Various materials have been suggested for this,
11 as described in U.S. Patent Nos. 3,472,931; 3,527,864; 3,896,238;
12 3,903,256; 3,952,099; 4,046,886; 4,130,643; 4,130,667; 4,299,826;
13 4,335,115; 4,343,798; 4,379,454; 4,405,616; 4,746,515; 4,788,062;
14 4,820,720; 4,863,738; 4,863,970; and 5,378,730; British Patent
15 No. 1,011,949; and Idson, "Percutaneous Absorption,"
16 J. Pharm. Sci. (1975) 64:901-924.

17 To be considered useful, a permeation enhancer should have the
18 ability to enhance the permeability of the skin for at least one and preferably a
19 significant number of drugs. More importantly, it should be able to enhance
20 the skin permeability such that the drug delivery rate from a reasonably sized
21 system (preferably 5-50cm²) is at therapeutically effective levels. Additionally,
22 the enhancer when applied to the skin surface, should be non-toxic, non-
23 irritating on prolonged exposure and under occlusion, and non-sensitizing on
24 repeated exposure. Preferably, it should be odorless and capable of
25 delivering drugs without producing burning or tingling sensations.

SUMMARY OF THE INVENTION

According to the present invention, it has been discovered that acyl lactylates are effective in enhancing the permeation of drugs through body surfaces and membranes generally, and through skin in particular. Importantly, the acyl lactylates of the present invention are able to enhance the permeability of drugs such that they can be delivered at therapeutically effective rates with reasonably sized transdermal delivery devices. Preferred acyl lactylate permeation enhancers of the present invention are caproyl lactic acid and lauroyl lactic acid.

Accordingly, the present invention provides a composition of matter for administration to a body surface or membrane to deliver at least one drug to the systemic circulation of a patient, at a therapeutically effective rate, by permeation through the body surface or membrane, comprising at least one drug and a permeation-enhancing amount of an acyl lactylate. The invention further provides a method for the transdermal coadministration of a drug at a therapeutically effective rate together with a skin permeation-enhancing amount of an acyl lactylate.

The system of the invention is preferably a transdermal drug delivery device comprising a matrix adapted to be placed in drug- and permeation enhancer-transmitting relation with the skin or mucosa. The system must be of a reasonable size useful for the application of the drug and the enhancer to a human body.

The invention is further directed to a composition of matter which optionally includes, in addition to the drug and acyl lactylate, one or more additional permeation enhancing compounds and to a method for the transdermal coadministration of such a composition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional view of one embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

FIG. 2 is a cross-sectional view of another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

FIG. 3 is a cross-sectional view of yet another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with this invention.

FIG. 4 is a graph of the flux of progesterone through human epidermis at 35° C, in vitro, from a mineral oil system with various permeation enhancers.

FIG. 5 is a graph of the flux of testosterone through human epidermis at 35° C, in vitro, from a mineral oil system with various permeation enhancers.

FIG. 6 is a graph of the flux of testosterone through human epidermis at 35° C, in vitro, from an EVA matrix system with various permeation enhancers.

DETAILED DESCRIPTION OF THE INVENTION

According to this invention, it has been discovered that acyl lactylates can be used to effectively enhance the permeability of drugs through body surfaces or membranes and particularly through the skin. Specifically, it has been found that acyl lactylates, when converted to a free acid form, enhance the permeability of the body surface or membrane to drugs or other biologically active agents such that therapeutically effective amounts of a drug or agent can be systemically delivered from reasonably sized devices at

1 therapeutically effective rates. Additionally, it has been found that water
2 dispersion of the acid form does not show corrosively low pH (pH 4.0-5.0):

3 It is believed that this invention has utility in connection with the
4 delivery of drugs within the broad class normally delivered through body
5 surfaces and membranes, including skin. In general, this includes therapeutic
6 agents in all of the major areas, including, but not limited to, ACE inhibitors,
7 adenoypophoseal hormones, adrenergic neuron blocking agents,
8 adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical
9 steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective
10 alpha-two-adrenergic agonists, analgesics, antipyretics and anti-inflammatory
11 agents, androgens, local and general anesthetics, antiaddictive agents,
12 antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic
13 agents, anticholinesterase agents, anticoagulants, antidiabetic agents,
14 antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents,
15 antiepileptic agents, antiestrogens, antifungal agents, antihypertensive
16 agents, antimicrobial agents, antimigraine agents, antimuscarinic agents,
17 antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet
18 agents, antiprogestins, antithyroid agents, antitussives, antiviral agents,
19 atypical antidepressants, azaspirodecanediones, barbituates,
20 benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-
21 adrenergic antagonists, selective beta-one-adrenergic antagonists, selective
22 beta-two-adrenergic agonists, bile salts, agents affecting volume and
23 composition of body fluids, butyrophenones, agents affecting calcification,
24 calcium channel blockers, cardiovascular drugs, catecholamines and
25 sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators,
26 dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids,
27 estrogens, ganglionic blocking agents, ganglionic stimulating agents,
28 hydantoins, agents for control of gastric acidity and treatment of peptic ulcers,
29 hematopoietic agents, histamines, histamine antagonists,

1 5-hydroxytryptamine antagonists, drugs for the treatment of
2 hyperlipoproteinemia, hypnotics and sedatives, immunosuppressive agents,
3 laxatives, methylxanthines, monoamine oxidase inhibitors, neuromuscular
4 blocking agents, organic nitrates, opiod analgesics and antagonists,
5 pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for
6 the treatment of psychiatric disorders, retinoids, sodium channel blockers,
7 agents for spasticity and acute muscle spasms, succinimides, thioxanthines,
8 thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of
9 tubular transport of organic compounds, drugs affecting uterine motility,
10 vasodilators, vitamins and the like.

11 Representative drugs include, by way of example and not for purposes
12 of limitation, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine,
13 nimodipine, nitredipine, verapamil, dobutamine, isoproterenol, carterolol,
14 labetalol, levobunolol, nadolol, penbutolol, pindolol, propranolol, sotalol,
15 timolol, acebutolol, atenolol, betaxolol, esmolol, metoprolol, albuterol,
16 bitolterol, isoetharine, metaproterenol, pirbuterol, ritodrine, terbutaline,
17 alclometasone, aldosterone, amcinonide, beclomethasone, dipropionate,
18 betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone,
19 desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol,
20 dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone,
21 fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone,
22 medrysone, 6 α -methylprednisolone, mometasone, paramethasone,
23 prednisolone, prednisone, tetrahydrocortisol, triamcinolone, benoxinate,
24 benzocaine, bupivacaine, chloroprocaine, cocaine, dibucaine, dyclonine,
25 etidocaine, lidocaine, mepivacaine, pramoxine, prilocaine, procaine,
26 proparacaine, tetracaine, alfentanil, chloroform, clonidine, cyclopropane,
27 desflurane, diethyl ether, droperidol, enflurane, etomidate, fentanyl,
28 halothane, isoflurane, ketamine hydrochloride, meperidine, methohexital,
29 methoxyflurane, morphine, propofol, sevoflurane, sufentanil, thiamylal,
30 thiopental, acetaminophen, allopurinol, apazone, aspirin, auranofin,

1 aurothioglucose, colchicine, diclofenac, diflunisal, etodolac, fenoprofen,
2 flurbiprofen, gold sodium thiomalate, ibuprofen, indomethacin, ketoprofen,
3 meclofenamate, mefenamic acid, meselamine, methyl salicylate,
4 nabumetone, naproxen, oxyphenbutazone, phenacetin, phenylbutazone,
5 piroxicam, salicylamide, salicylate, salicylic acid, salsalate, sulfasalazine,
6 sulindac, tolmetin, acetophenazine, chlorpromazine, fluphenazine,
7 mesoridazine, perphenazine, thioridazine, trifluorperazine, triflupromazine,
8 disopyramide, encainide, flecainide, indecainide, mexiletine, moricizine,
9 phenytoin, procainamide, propafenone, quinidine, tocainide, cisapride,
10 domperidone, dronabinol, haloperidol, metoclopramide, nabilone,
11 prochlorperazine, promethazine, thiethylperazine, trimethobenzamide,
12 buprenorphine, butorphanol, codeine, dezocine, diphenoxylate, drocode,
13 hydrocodone, hydromorphone, levallorphan, levorphanol, loperamide,
14 meptazinol, methadone, nalbuphine, nalmefene, nalorphine, naloxone,
15 naltrexone, oxybutynin, oxycodone, oxymorphone, pentazocine,
16 propoxyphene, isosorbide dinitrate, nitroglycerin, theophylline, phenylephrine,
17 ephedrine, pilocarpine, furosemide, tetracycline, chlorpheniramine, ketorolac,
18 bromocriptine, guanabenz, prazosin, doxazosin, and flufenamic acid.

19 Other representative drugs include benzodiazepines, such as
20 alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam,
21 clorazepate, demoxepam, diazepam, flumazenil, flurazepam, halazepam,
22 lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam,
23 quazepam, temazepam, triazolam, and the like; an antimuscarinic agent such
24 as anisotropine, atropine, clidinium, cyclopentolate, dicyclomine, flavoxate,
25 glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide,
26 mepenzolate, methantheline, oxyphencyclimine, pirenzepine, propantheline,
27 scopolamine, telenzepine, tridihexethyl, tropicamide, and the like; an estrogen
28 such as chlorotrianisene, siethylstilbestrol, methyl estradiol, estrone, estrone
29 sodium sulfate, estropipate, mestranol, quinestrol, sodium equilin sulfate,
30 17 β -estradiol (or estradiol), semi-synthetic estrogen derivatives such as the

1 esters of natural estrogen, such as estradiol-17 β -enanthate, estradiol-17 β -
2 valerate, estradiol-3-benzoate, estradiol-17 β -undecenoate, estradiol 16,
3 17-hemisuccinate or estradiol-17 β -cypionate, and the 17-alkylated estrogens,
4 such as ethinyl estradiol, ethinyl estradiol-3- isopropylsulphonate, and the
5 like; an androgen such as danazol, fluoxymesterone, methandrostenolone,
6 methyltestosterone, nandrolone decanoate, nandrolone phenpropionate,
7 oxandrolone, oxymetholone, stanozolol, testolactone, testosterone,
8 testosterone cypionate, testosterone enanthate, testosterone propionate,
9 and the like; or a progestin such as ethynodiol diacetate, gestodene,
10 hydroxyprogesterone caproate, levonorgestrel, medroxyprogesterone
11 acetate, megestrol acetate, norethindrone, norethindrone acetate,
12 norethynodrel, norgestrel, progesterone, and the like.

13 Administration of the drug according to the invention comprises
14 administering the drug at a therapeutically effective rate to an area of a body
15 surface or membrane and simultaneously administering an acyl lactylate to
16 the area of the body surface or membrane at a rate sufficient to substantially
17 increase the permeability of the area to the drug formulation.

18 According to the invention, an acyl lactylate permeation enhancer and
19 the drug to be delivered are placed in drug- and acyl lactylate-transmitting
20 relationship to the appropriate body surface, preferably in a carrier therefor,
21 and maintained in place for the desired period of time. The drug and acyl
22 lactylate are typically dispersed within a physicochemically and biologically
23 compatible matrix or carrier which may be applied directly to the body surface
24 or skin as an ointment, gel, cream, suppository or sublingual or buccal tablet,
25 for example, but are more preferably administered from a transdermal
26 therapeutic delivery device as more fully described below. When used in the
27 form of a liquid, ointment, cream, or gel applied directly to the skin, it is
28 preferable, although not required, to occlude the site of administration.
29 Such compositions can also contain other permeation enhancers, stabilizers,
30 dyes, diluents, pigments, vehicles, inert fillers, excipients, gelling agents,

1 vasoconstrictors, and other components of typical compositions as are known
2 to the art.

3 The acyl lactylates of this invention have a permeation-enhancing
4 effect on the transport of drugs through body surface tissues generally,
5 in addition to the skin. However, because skin is one of the most effective
6 body barriers to the permeation of foreign substances, the effect of acyl
7 lactylates on skin permeation makes it extremely useful in transdermal
8 delivery. The following description of embodiments of the invention is
9 therefore directed primarily to improving systemic delivery of these drugs by
10 permeation through the skin.

11 It may be desirable in certain instances or with certain drugs to include
12 one or more additional permeation enhancers in combination with the acyl
13 lactylate. Thus, in certain embodiments of the present invention, a second
14 permeation enhancer is included together with the drug and acyl lactylate
15 permeation enhancer. This second enhancer may be selected from those
16 compounds that have a permeation-enhancing effect with the drug and are
17 compatible with the drug and with the acyl lactylate. For example, the second
18 permeation enhancer may be a monoglyceride or mixture of monoglycerides
19 of fatty acids such as glycerol monolaurate (GML) or glycerol monooleate
20 (GMO), lauramide diethanolamine (LDEA), esters of fatty acids having from
21 about 10 to 20 carbon atoms, and/or a lower C₁₋₄ alcohol such as ethanol or
22 isopropanol.

23 Typically, monoglycerides have been available as a mixture of
24 monoglycerides of fatty acids with one monoglyceride being the principal
25 component, from which component the mixture derives its name.
26 For example, one commercial monoglyceride is Emerest 2421 glycerol
27 monooleate (Emery Division, Quantum Chemical Corp.), which is a mixture of
28 glycerol oleates with a glycerol monooleate content of 58% and a total
29 monoesters content of 58%. Other examples of commercial monoglycerides
30 are Myverol 1899K glycerol monooleate (Eastman Chemical Products) which

1 has a glycerol monooleate content of 61% and a total monoesters content of
2 93%, and Myverol 1892K glycerol monolinoleate which has a glycerol
3 monolinoleate content of 68% and a minimum total monoesters content of
4 90%. The monoesters are chosen from those with from 10 to 20 carbon
5 atoms. The fatty acids may be saturated or unsaturated and include,
6 for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid and
7 palmitic acid. Monoglyceride permeation enhancers include glycerol
8 monooleate, glycerol monolaurate and glycerol monolinoleate, for example.
9 In a presently preferred embodiment of this invention, the second permeation
10 enhancer is a monoglyceride or a mixture of monoglycerides of unsaturated
11 fatty acids, and more preferred is glycerol monolaurate (GML). As used
12 herein and in the appended claims, the term "monoglyceride" refers to a
13 monoglyceride or a mixture of monoglycerides of fatty acids.

14 It has been seen that glycerol monooleate having a total monoesters
15 content of less than about 65% interacts adversely with known adhesive
16 materials to such an extent that the adhesive cannot function to maintain a
17 delivery device on the skin. Therefore, when an in-line adhesive is present as
18 a part of the device of the invention so that a permeation enhancer must pass
19 through the adhesive, and when glycerol monooleate is utilized as the second
20 permeation enhancer, the glycerol monooleate must have a total monoesters
21 content of at least 65%.

22 The permeation-enhancing mixture is dispersed throughout the matrix
23 or carrier, preferably at a concentration sufficient to provide permeation-
24 enhancing amounts of enhancer in the reservoir throughout the anticipated
25 administration period. Where there is an additional, separate permeation
26 enhancer matrix layer as well, as in FIG. 2, the permeation enhancer normally
27 is present in the separate reservoir in excess of saturation.

28 One embodiment of a transdermal delivery device of the present
29 invention is illustrated in FIG. 1. In FIG. 1, device 1 is comprised of a drug-
30 and acyl lactylate-containing reservoir ("drug reservoir") 2 which is preferably

1 in the form of a matrix containing the drug and the enhancer dispersed
2 therein. In those embodiments which include a mixture of permeation
3 enhancers, drug reservoir 2 also includes these additional enhancers.
4 A backing layer 3 is provided adjacent one surface of drug reservoir 2.
5 Adhesive overlay 4 maintains the device 1 on the skin and may be fabricated
6 together with, or provided separately from, the remaining elements of the
7 device. With certain formulations, the adhesive overlay 4 may be preferable
8 to an in-line contact adhesive, such as adhesive layer 28 as shown in FIG. 3.
9 Backing layer 3 is preferably slightly larger than drug reservoir 2, and in this
10 manner prevents the materials in drug reservoir 2 from adversely interacting
11 with the adhesive in overlay 4. A strippable or removable liner 5 is also
12 provided with device 1 and is removed just prior to application of device 1 to
13 the skin.

14 Figure 2 illustrates another embodiment of the invention, device 10,
15 shown in placement on the skin 17. In this embodiment, the transdermal
16 delivery device 10 comprises a multi-laminate drug formulation/enhancer
17 reservoir 11 having at least two zones 12 and 14. Zone 12 consists of a drug
18 reservoir substantially as described with respect to FIG. 1. Zone 14
19 comprises a permeation enhancer reservoir which is preferably made from
20 substantially the same matrix as is used to form zone 12. Zone 14 comprises
21 an acyl lactylate dispersed throughout, preferably in excess of saturation, and
22 is substantially free of any undissolved drug. One or more additional
23 permeation enhancers may optionally be included in zone 14 as well.
24 A rate-controlling membrane 13 for controlling the release rate of the acyl
25 lactylate and, optionally, any additional enhancers from zone 14 to zone 12 is
26 placed between the two zones. A rate-controlling membrane (not shown) for
27 controlling the release rate of the enhancer from zone 12 to the skin may also
28 optionally be utilized and would be present between the skin 17 and zone 12.

1 The rate-controlling membrane may be fabricated from permeable,
2 semipermeable or microporous materials which are known in the art to control
3 the rate of agents into and out of delivery devices and having a permeability
4 to the permeation enhancer lower than that of zone 12. Suitable materials
5 include, but are not limited to, polyethylene, polyvinyl acetate and ethylene
6 vinyl acetate copolymers.

7 An advantage of the device described in FIG. 2 is that the drug-loaded
8 zone 12 is concentrated at the skin surface rather than throughout the entire
9 mass of the reservoir 11. This functions to reduce the amount of drug in the
10 device while maintaining an adequate supply of the permeation enhancer
11 or mixture.

12 Superimposed over the drug formulation/enhancer -reservoir 11 of
13 device 10 is a backing 15 and an adhesive overlay 16 as described above
14 with respect to FIG. 1. In addition, a strippable liner (not shown) would
15 preferably be provided on the device prior to use as described with respect to
16 FIG. 1 and removed prior to application of the device 10 to the skin 17.

17 In the embodiments of FIGS. 1 and 2, the carrier or matrix material has
18 sufficient viscosity to maintain its shape without oozing or flowing.
19 If, however, the matrix or carrier is a low viscosity flowable material,
20 the composition can be fully enclosed in a dense non-porous or microporous
21 skin-contacting membrane, as known to the art from U.S. Pat. No. 4,379,454
22 (noted above), for example.

23 An example of a presently preferred transdermal delivery device is
24 illustrated in FIG. 3. In FIG. 3, transdermal delivery device 20 comprises a
25 drug reservoir 22 containing together the drug and the acyl lactylate
26 permeation enhancer. Optionally, one or more additional permeation
27 enhancers may also be included in drug reservoir 22. Reservoir 22 is
28 preferably in the form of a matrix containing the drug and the enhancer
29 dispersed therein. Reservoir 22 is sandwiched between a backing layer 24,
30 which is impermeable to both the drug and the acyl lactylate, and an in-line

1 contact adhesive layer 28. In FIG. 3, the drug reservoir 22 is formed of a
2 material, such as a rubbery polymer, that is sufficiently viscous to maintain its
3 shape. The device 20 adheres to the surface of the skin 17 by means of the
4 contact adhesive layer 28. The adhesive for layer 28 should be chosen so
5 that it is compatible and does not interact with any of the drug or, in particular,
6 the acyl lactylate permeation enhancer. The adhesive layer 28 may optionally
7 contain permeation enhancer and/or drug. A strippable liner (not shown) is
8 normally provided along the exposed surface of adhesive layer 28 and is
9 removed prior to application of device 20 to the skin 17. In an alternative
10 embodiment, a rate-controlling membrane (not shown) is present and the
11 drug reservoir 22 is sandwiched between backing layer 24 and the rate-
12 controlling membrane, with adhesive layer 28 present on the skin-side of the
13 rate-controlling membrane.

14 Various materials suited for the fabrication of the various layers of the
15 transdermal devices of FIGS. 1, 2 or 3 are known in the art or are disclosed in
16 the aforementioned transdermal device patents previously incorporated
17 herein by reference.

18 The matrix making up the drug/acyl lactylate permeation enhancer
19 reservoir can be a gel or a polymer. Suitable materials should be compatible
20 with the drug and enhancer and any other components in the system.
21 The matrix may be aqueous or non-aqueous based. Aqueous formulations
22 typically comprise water or water/ethanol and about 1-5 wt% of a gelling
23 agent, an example being a hydrophilic polymer such as hydroxyethylcellulose
24 or hydroxypropylcellulose. Typical non-aqueous gels are comprised of
25 silicone fluid or mineral oil. Mineral oil based gels also typically contain 1-2
26 wt% of a gelling agent such as colloidal silicon dioxide. The suitability of a
27 particular gel depends upon the compatibility of its constituents with the drug
28 and the permeation-enhancing mixture in addition to any other components in
29 the formulation.

1 When using a non-aqueous based formulation, the reservoir matrix is
2 preferably composed of a hydrophobic polymer. Suitable polymeric matrices
3 are well known in the transdermal drug delivery art, and examples are listed
4 in the above-named patents previously incorporated herein by reference.
5 A typical laminated system would consist essentially of a polymeric
6 membrane and/or matrix such as ethylene vinyl acetate (EVA) copolymers,
7 such as those described in US Patent No. 4,144,317, preferably having a vinyl
8 acetate content in the range of from about 9% to about 60% and more
9 preferably about 9% to 40% vinyl acetate. Polyisobutylene/oil polymers
10 containing from 4-25% high molecular weight polyisobutylene and 20-81%
11 low molecular weight polyisobutylene with the balance being an oil such as
12 mineral oil or polyisobutylenes may also be used as the matrix material.

13 In addition to a drug and acyl lactylate, which are essential to the
14 invention, the matrix may also contain stabilizers, dyes, pigments, inert fillers,
15 tackifiers, excipients and other conventional components of transdermal
16 delivery devices as are known in the art.

17 The amounts of the drug that are present in the therapeutic device,
18 and that are required to achieve a therapeutic effect, depend on many
19 factors, such as the minimum necessary dosage of the particular drug;
20 the permeability of the matrix, of the adhesive layer and of the rate-controlling
21 membrane, if present; and the period of time for which the device will be fixed
22 to the skin. There is, in fact, no upper limit to the maximum amounts of drug
23 present in the device. The minimum amount of each drug is determined by
24 the requirement that sufficient quantities of drug must be present in the device
25 to maintain the desired rate of release over the given period of application.

26 The drug is generally dispersed through the matrix at a concentration
27 in excess of saturation, i.e. at unit activity. The amount of excess is
28 determined by the intended useful life of the system. However, the drug may
29 be present at initial levels below saturation without departing from this
30 invention. Generally, the drug may be present at initially subsaturated levels

1 when: 1) the skin flux of the drug is sufficiently low such that the reservoir
2 drug depletion is slow and small; 2) non-constant delivery of the drug is
3 desired or acceptable; and/or 3) saturation of the reservoir is achieved in use
4 due to migration of water into the reservoir from the skin, where water is
5 abundantly available.

6 The acyl lactylate permeation enhancer is dispersed throughout the
7 matrix, preferably at a concentration sufficient to provide permeation-
8 enhancing concentrations of enhancer in the reservoir throughout the
9 anticipated administration period.

10 In certain embodiments of the invention, one or more additional
11 permeation enhancers, such as a monoglyceride or mixture of
12 monoglycerides of fatty acids including glycerol monolaurate (GML) and
13 glycerol monooleate (GMO), lauramide diethanolamine (LDEA), esters of fatty
14 acids having from about 10 to 20 carbon atoms, and/or a lower C₁₋₄ alcohol
15 such as ethanol or isopropanol, may also be dispersed throughout the matrix,
16 preferably at a concentration sufficient to provide permeation-enhancing
17 concentrations of enhancer in the drug reservoir throughout the anticipated
18 administration period.

19 In the present invention, the drug is delivered through the skin or other
20 body surface at a therapeutically effective rate (that is, a rate that provides an
21 effective therapeutic result) and the acyl lactylate permeation enhancer is
22 delivered at a permeation-enhancing rate (that is, a rate that provides
23 increased permeability of the application site to the drug) for a predetermined
24 time period.

25 A preferred embodiment of the present invention is a monolith such as
26 that illustrated in FIG. 3 (either with or without a rate-controlling membrane)
27 wherein reservoir 22 comprises, by weight, 30- 90% polymer (preferably EVA
28 with a vinyl acetate content of 40%), 0.01-40% drug, and 1-70% of an acyl
29 lactylate. The in-line adhesive layer 28 contains an adhesive which is
30 compatible with the permeation enhancer. In another preferred embodiment

1 of the invention, a monolith such as that in FIG. 3 includes reservoir 22
2 comprising, by weight, 30-90% polymer (preferably EVA with a vinyl acetate
3 content of 40%), 0.01-40% drug, 1-70% acyl lactylate, and 1-45% of a second
4 permeation enhancer, preferably GML.

5 The devices of this invention can be designed to effectively deliver a
6 drug for an extended time period of up to 7 days or longer. Seven days is
7 generally the maximum time limit for application of a single device because
8 the skin site may be affected by a period of occlusion greater than 7 days,
9 or other problems such as the system or edges of the system lifting off of the
10 skin may be encountered over such long periods of application. Where it is
11 desired to have drug delivery for greater than 7 days (such as, for example,
12 when a hormone is being applied for a contraceptive effect), when one device
13 has been in place on the skin for its effective time period, it is replaced with a
14 fresh device, preferably on a different skin site.

15 The transdermal therapeutic devices of the present invention are
16 prepared in a manner known in the art, such as by those procedures,
17 for example, described in the transdermal device patents listed previously
18 herein. The following examples are offered to illustrate the practice of the
19 present invention and are not intended to limit the invention in any manner.

20

21

EXAMPLE 1

22

23 Several test samples were made to measure the progesterone flux
24 through human cadaver skin from donor vehicles containing progesterone at
25 saturation in mineral oil. The progesterone vehicle was also mixed with 20%
26 by weight caproyl lactic acid or lauroyl lactic acid, or dispersed with 1.1%
27 by weight glycerol monolaurate. Transdermal fluxes were obtained using
28 human epidermis at 35° C in standard diffusion cells. As seen in Figure 4,
29 the progesterone mixtures with caproyl lactic acid and lauroyl lactic acid
30 demonstrated superior flux of progesterone through skin.

EXAMPLE 2

Several test samples were made to measure the testosterone flux through human cadaver skin. Testosterone saturated in mineral oil was used as a control, and was compared with mixtures including 12% GML / 7% caproyl lactic acid, or 12% GML / 7% lauroyl lactic acid. Transdermal fluxes were obtained using human epidermis at 35° C in standard diffusion cells. As demonstrated in Figure 5, the solutions containing the GML/acyl lactylate mixtures resulted in a testosterone flux through skin at least double that of the control.

EXAMPLE 3

The drug/permeation enhancer reservoirs were prepared by mixing ethylene vinyl acetate having a vinyl acetate content of 40 percent ("EVA 40", USI Chemicals, Illinois) in an internal mixer (Brabender type mixer) until the EVA 40 pellets fused. Testosterone, lauroyl lactic acid (LLA), caproyl lactic acid (CLA), GML, lactic acid (LA), M-DEA, L-DEA, or lauryl lactate (LL) were then added as shown in Table 1. The mixture was blended, cooled and calendered to a 5 mil thick film.

The film was then laminated to a Medpar® (3M) backing on one side and an acrylate contact adhesive (3M) on the opposite side. The laminate was then cut into 1.98 cm² circles using a steel punch.

Circular pieces of human epidermis were mounted on horizontal permeation cells with the stratum corneum facing the donor compartment of the cell. The release liner of the laminate was removed and the systems were centered over the stratum corneum side of the epidermis. The cells were then masked. A known volume of receptor solution (20 ml) was

1 equilibrated at 35 °C and placed in the receptor compartment. Air bubbles
2 were removed from the receptor compartment, the cell was capped and
3 placed in a water bath shaker at 35 °C.

Table 1

Drug/ Permeation Enhancer Reservoir (wt %)

RESERVOIR FORMULATION	WEIGHT PERCENT
Testosterone/LLA/GML/EVA 40	10/20/20/50
Testosterone/CLA/ L-DEA/EVA 40	10/20/20/50
Testosterone/LL/LA/GML/EVA 40	10/12/3/20/55
Testosterone/LL/LA/L-DEA/EVA 40	10/12/3/20/55
Testosterone/LLA/M-DEA/EVA 40	10/20/20/50
Testosterone/LL/LA/M-DEA/EVA 40	10/12/3/20/55
Testosterone/EVA 40	2/98

7
8 At given time intervals, the entire receptor solution was removed from
9 the cells and replaced with an equal volume of fresh receptor solutions
10 previously equilibrated at 35 °C. The receptor solutions are stored in capped
11 vials at room temperature until assayed for testosterone content by HPLC.
12 From the drug concentration and the volume of the receptor solutions, the
13 area of permeation and the time interval, the flux of the drug through the
14 epidermis was calculated as follows: (drug concentration X volume of
15 receptor)/(area X time) = flux ($\mu\text{g}/\text{cm}^2 \cdot \text{hr}$). The flux of the testosterone
16 achieved from the various systems is shown in Figure 6. As demonstrated in
17 Figure 6, formulations comprising mixtures including lauroyl lactic acid or
18 caproyl lactic acid resulted in superior flux of testosterone through the skin.

1 This invention has been described in detail with particular reference to certain
2 preferred embodiments thereof, but it will be understood that variations and
3 modifications can be effected within the spirit and scope of
4 the invention.

1 What is claimed is:

2

3 1. A composition of matter for transdermally delivering a drug to
4 the systemic circulation of a patient by permeation through a body surface or
5 membrane comprising, in combination:

6 (a) a drug; and

7 (b) a permeation-enhancing amount of an acyl lactylate permeation
8 enhancer sufficient to substantially increase the permeability of the body
9 surface or membrane to the drug in order to systemically deliver said drug to
10 a patient at a therapeutically effective rate, wherein the drug and acyl lactylate
11 permeation enhancer are dispersed within a pharmaceutically acceptable
12 carrier.

13 2. A composition according to claim 1 wherein the acyl lactylate is
14 caproyl lactic acid.

15 3. A composition according to claim 1 wherein the acyl lactylate is
16 lauroyl lactic acid.

17 4. A composition according to claim 1 wherein the acyl lactylate
18 permeation enhancer is combined with a permeation-enhancing amount of
19 one or more of the permeation enhancers selected from the group consisting
20 of monoglycerides or mixtures of monoglycerides of fatty acids, lauramide
21 diethanolamine, esters of fatty acids having from about 10 to 20 carbon
22 atoms, and lower C₁₋₄ alcohols.

23 5. A composition according to claim 1 wherein the acyl lactylate
24 permeation enhancer is combined with a permeation-enhancing amount of
25 glycerol monolaurate.

1 6. A device (1,20) for the transdermal administration of a drug to
2 the systemic circulation of a patient at a therapeutically effective rate, by
3 permeation through a body surface or membrane, comprising:

4 (a) a reservoir (2,22) comprising a drug and a permeation enhancing-
5 amount of an acyl lactylate permeation enhancer ; and

6 (b) means for maintaining (4,28) said reservoir in drug- and
7 permeation enhancer- transmitting relation with the body surface or
8 membrane, wherein said drug is delivered to the systemic circulation of a
9 patient at a therapeutically effective rate.

10 7. A device according to claim 6 wherein the acyl lactylate is
11 caproyl lactic acid.

12 8. A device according to claim 6 wherein the acyl lactylate is
13 lauroyl lactic acid.

14 9. A device according to claim 6 wherein the drug is testosterone.

15 10. A device according to claim 6 wherein the drug is progesterone.

16 11. A device according to claim 6 wherein the acyl lactylate
17 permeation enhancer is combined with a permeation-enhancing amount of
18 one or more of the permeation enhancers selected from the group consisting
19 of monoglycerides or mixtures of monoglycerides of fatty acids, lauramide
20 diethanolamine, esters of fatty acids having from about 10 to 20 carbon
21 atoms, and lower C₁₋₄ alcohols.

22 12. A device (10) for the transdermal administration of a drug to the
23 systemic circulation of a patient at a therapeutically effective rate,
24 by permeation through a body surface or membrane, comprising:

25 (a) a first reservoir (12) comprising a drug and a permeation-
26 enhancing amount of an acyl lactylate permeation enhancer;

27 (b) a second reservoir (14) comprising an additional amount of said
28 permeation enhancer and substantially free of said drug;

29 (c) a rate controlling membrane (13) between the first reservoir and
30 the second reservoir;

1 (d) means for maintaining (16) said first and second reservoirs in drug-
2 and permeation enhancer- transmitting relation with the body surface or
3 membrane, wherein the drug is delivered to the systemic circulation of a
4 patient at a therapeutically effective rate.

5 13. A device according to claim 10 wherein the acyl lactylate is
6 caproyl lactic acid.

7 14. A device according to claim 10 wherein the acyl lactylate is
8 lauroyl lactic acid.

9 15. A device according to claim 10 wherein the drug is testosterone.

10 16. A device according to claim 10 wherein the drug is
11 progesterone.

12 17. A device according to claim 10 wherein the acyl lactylate
13 permeation enhancer is combined with a permeation-enhancing amount of
14 one or more of the permeation enhancers selected from the group consisting
15 of monoglycerides or mixtures of monoglycerides of fatty acids, lauramide
16 diethanolamine, esters of fatty acids having from about 10 to 20 carbon
17 atoms, and lower C₁₋₄ alcohols.

18 18. A method for the transdermal administration of a drug to the
19 systemic circulation of a patient, at a therapeutically effective rate, by
20 permeation through a body surface or membrane, comprising:

21 (a) simultaneously administering, to the body surface or membrane,
22 a drug; and

23 (b) a permeation-enhancing amount of an acyl lactylate permeation
24 enhancer sufficient to substantially increase the permeability of the body
25 surface or membrane to the drug in order to systemically deliver said drug to
26 a patient at a therapeutically effective rate.

1 19. A method according to claim 18 further comprising
2 simultaneously coadministering a permeation-enhancing amount of one or
3 more of the permeation enhancers selected from the group consisting of
4 monoglycerides or mixtures of monoglycerides of fatty acids, lauramide
5 diethanolamine, esters of fatty acids having from about 10 to 20 carbon
6 atoms, and lower C₁₋₄ alcohols.

7 20. A method according to claim 18 wherein the acyl lactylate is
8 lauroyl lactic acid.

9 21. A method according to claim 18 wherein the acyl lactylate is
10 caproyl lactic acid.

11 22. A method according to claim 18 wherein the drug is
12 testosterone.

13 23. A method according to claim 18 wherein the drug is
14 progesterone.

15 24. A method according to claim 18 wherein the drug is
16 administered to the systemic circulation of said patient at a therapeutically
17 effective rate throughout a substantial portion of an administration period of at
18 least about 10 hours.

19 25. A method for the transdermal administration of a drug, the
20 method comprising the step of placing a transdermal delivery device (1,20)
21 onto a body surface or membrane of a person, the transdermal delivery
22 device comprising:

23 (a) a reservoir (2,22) comprising a drug and a permeation-enhancing
24 amount of an acyl lactylate permeation enhancer; and

25 (b) means for maintaining (4,28) said reservoir in drug- and
26 permeation enhancer- transmitting relation with the body surface or
27 membrane, wherein the drug is delivered to the systemic circulation of a
28 patient at a therapeutically effective rate.

- 1 26. A method for the transdermal administration of a drug, the
2 method comprising the step of placing a transdermal delivery device (10)
3 onto a body surface or membrane of a person, the transdermal delivery
4 device comprising:
- 5 (a) a first reservoir (10) comprising a drug and a permeation-
6 enhancing amount of an acyl lactylate permeation enhancer; and
- 7 (b) a second reservoir (14) comprising an additional amount of said
8 permeation enhancer and substantially free of said drug;
- 9 (c) a rate controlling membrane (13) between the first reservoir and
10 the second reservoir;
- 11 (d) means for maintaining (16) said first and second reservoirs in drug-
12 and permeation enhancer- transmitting relation with the body surface or
13 membrane, wherein the drug is delivered to the systemic circulation of a
14 patient at a therapeutically effective rate.

1 / 5

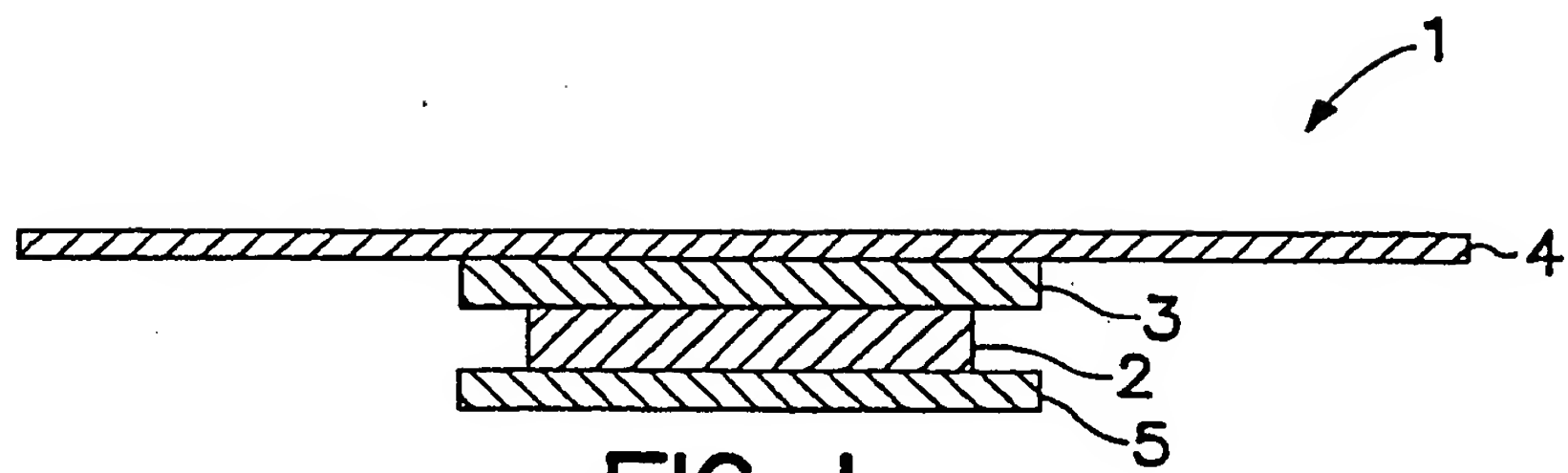


FIG. 1

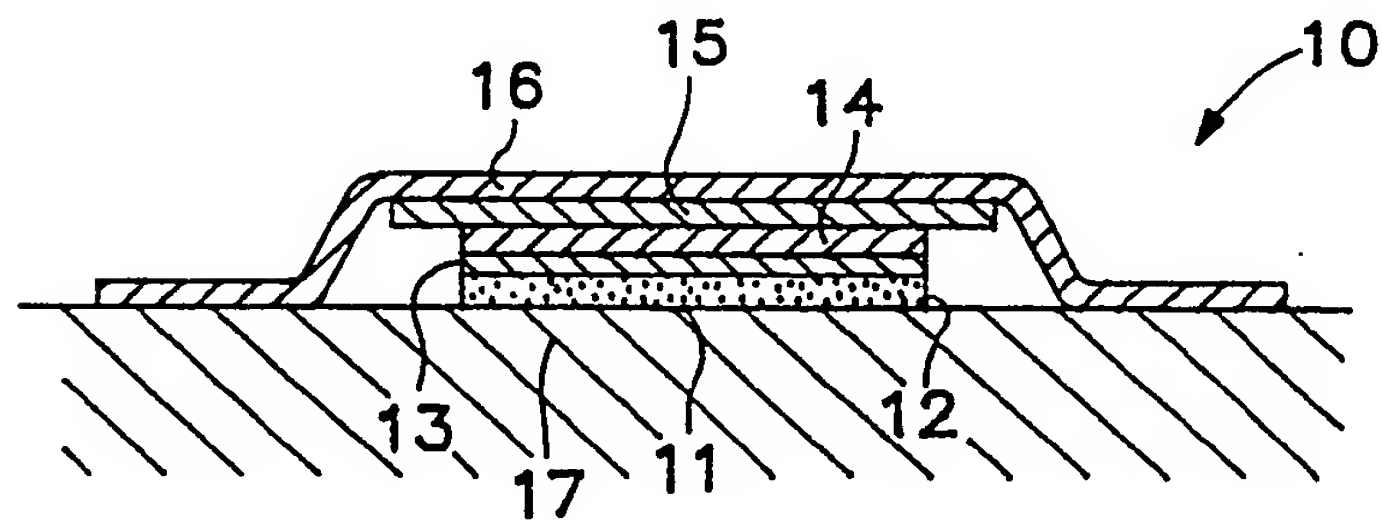


FIG. 2

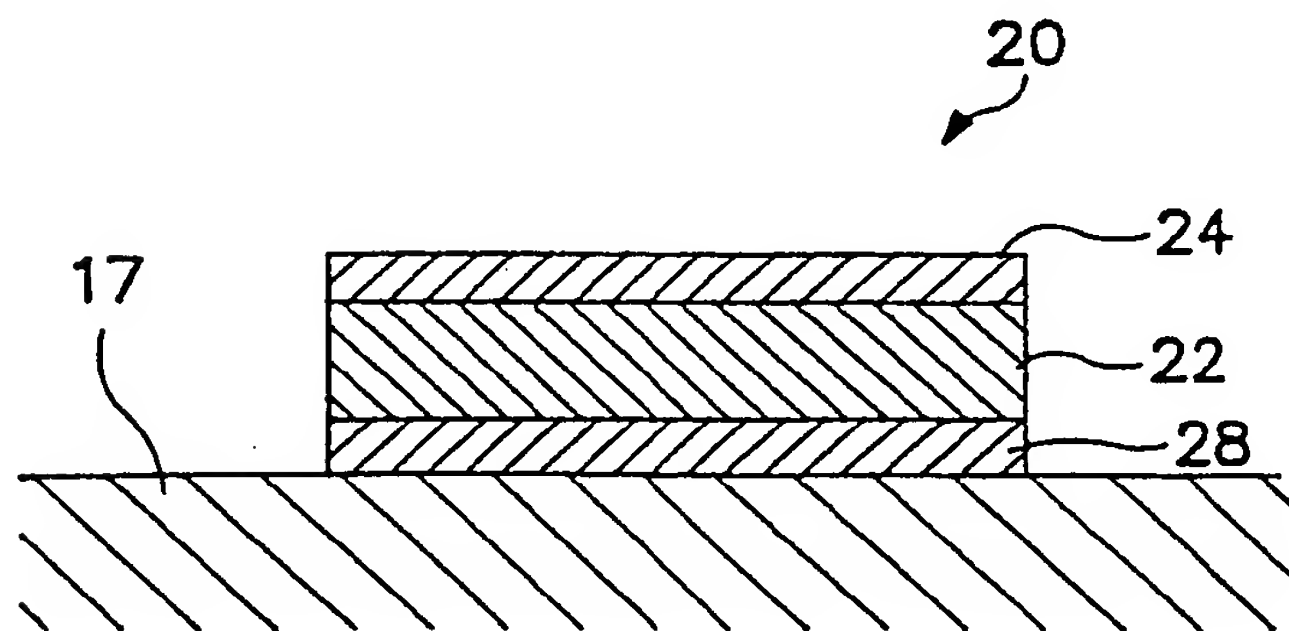
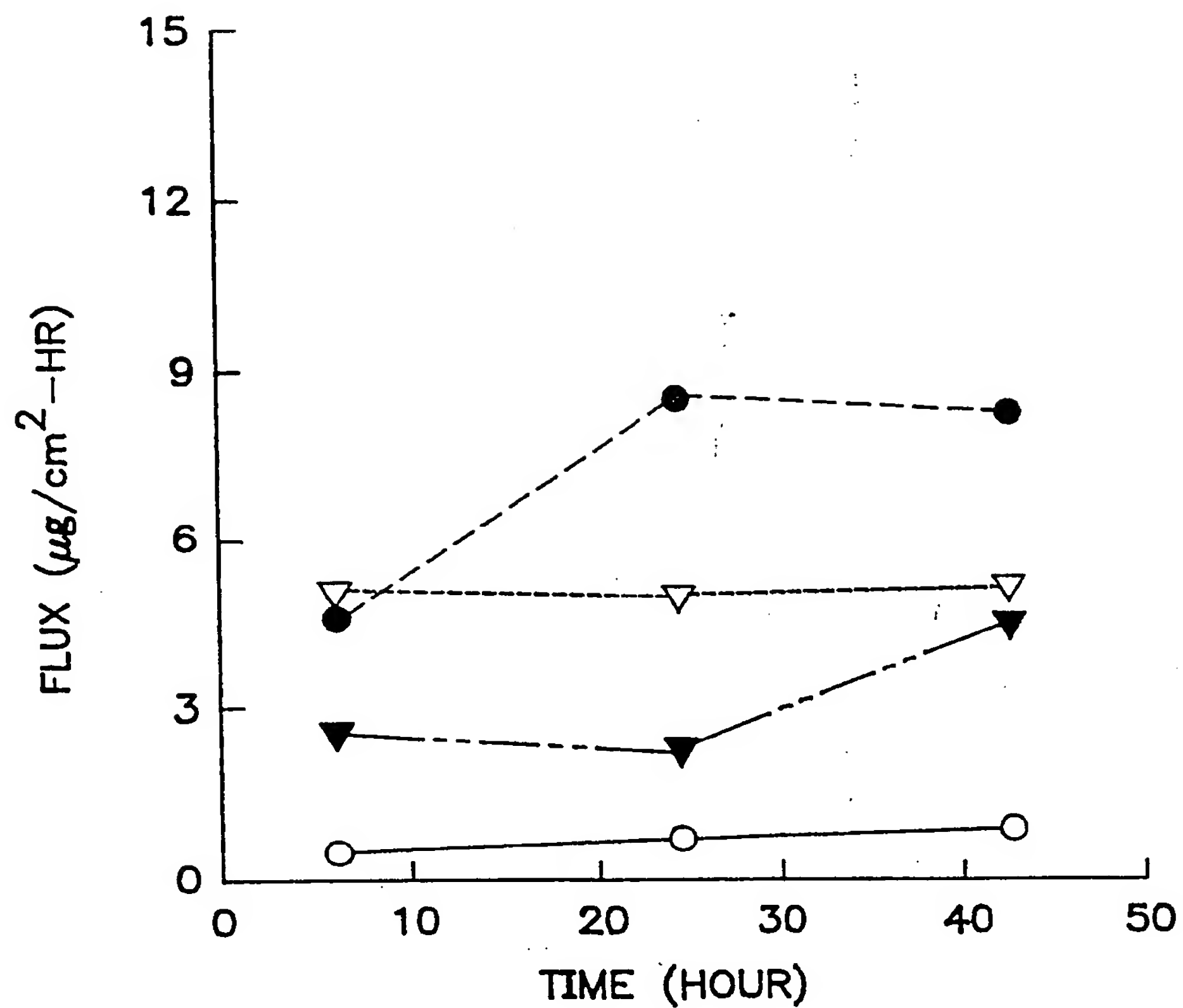


FIG. 3

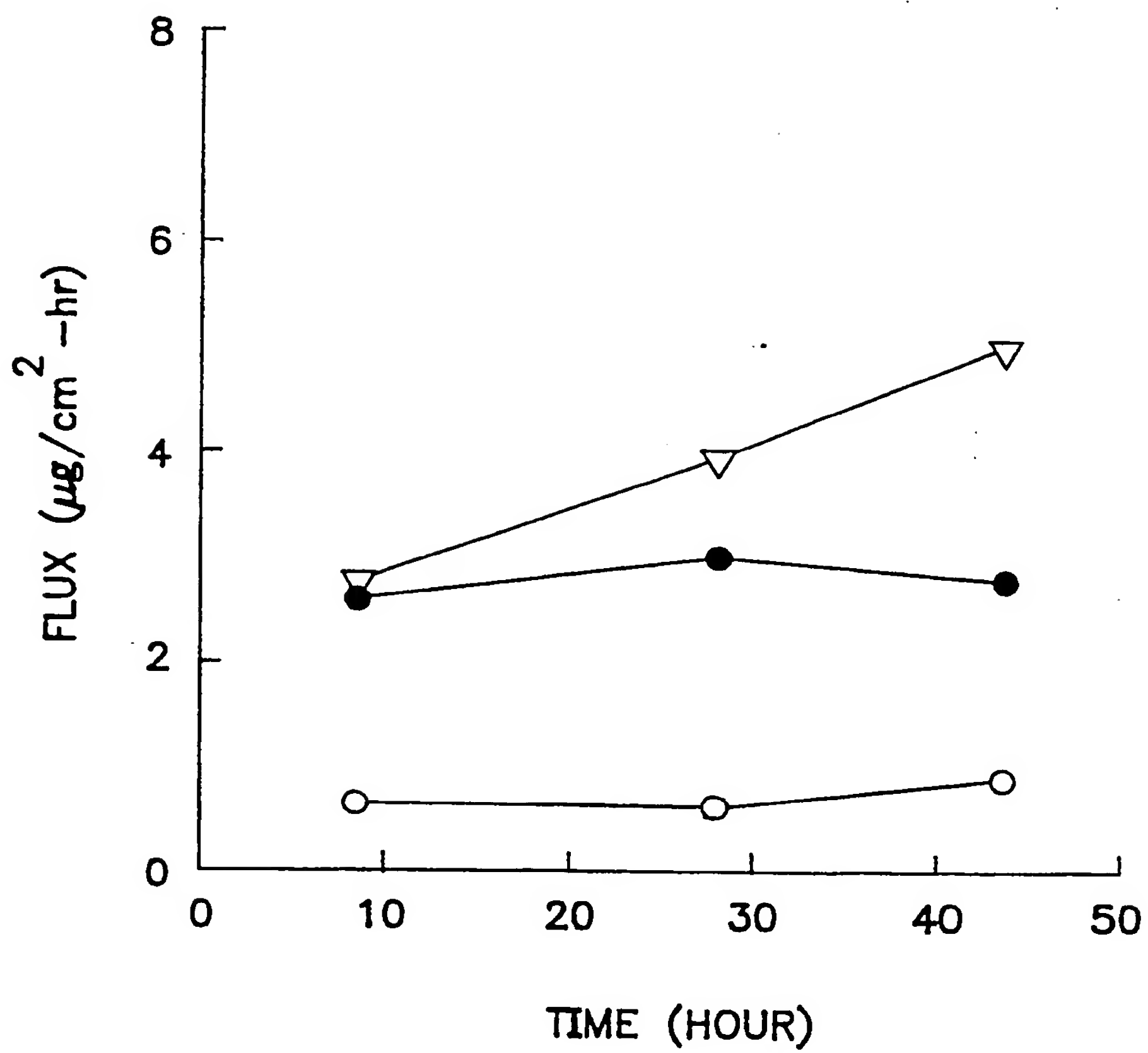
2 / 5



- CONTROL: PROGESTERONE SATURATED IN M.O.
● CAPROYL LACTYLIC ACID 20% IN M.O.
▽ LAUROYL LACTYLIC ACID 20% IN M.O.
▼ GML 1.1%(DISPERSED) IN M.O.

FIG. 4

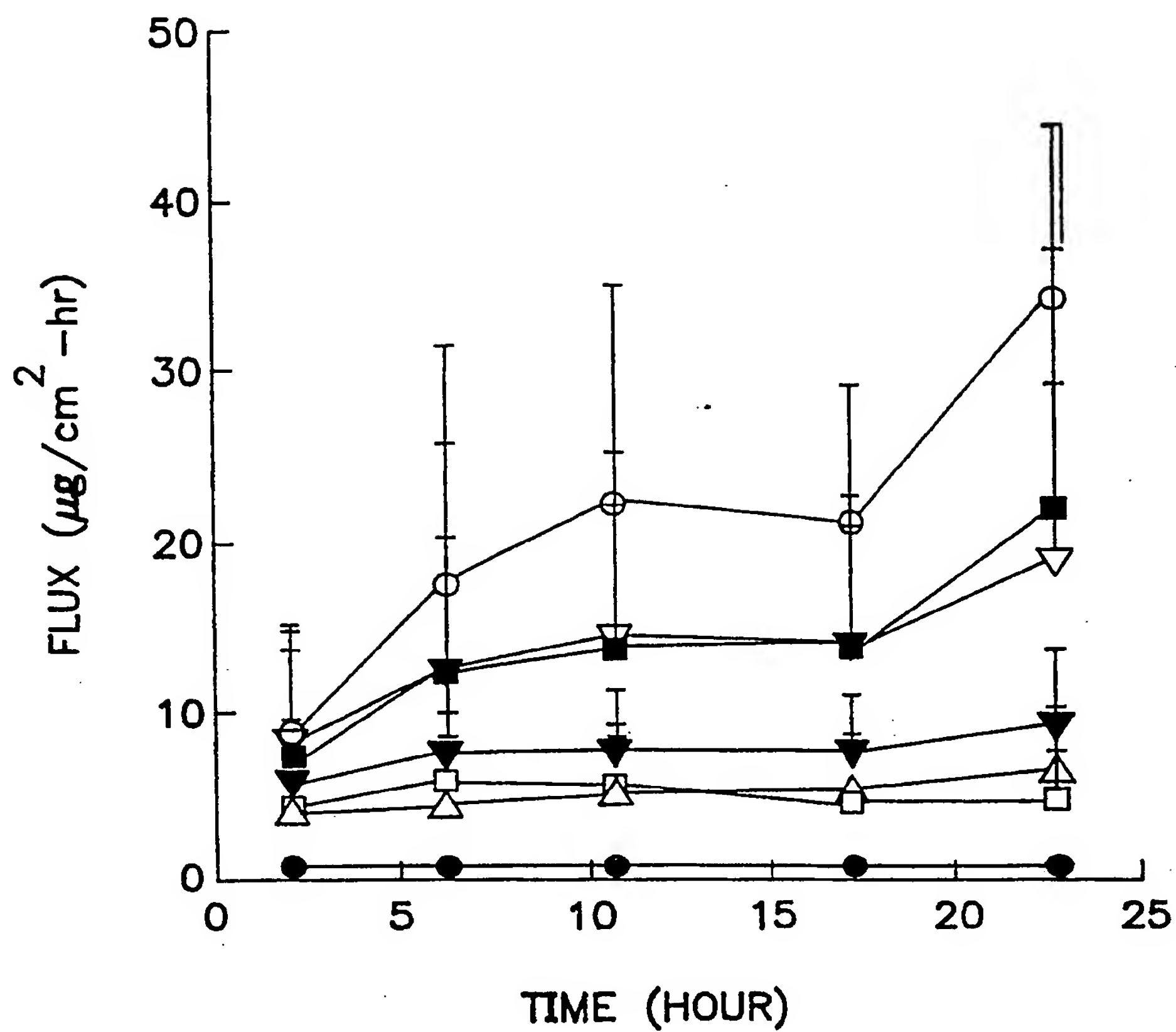
3 / 5



○ CONTROL: TESTOSTERONE SATURATED IN M.O.
● GML 12%/CAPROYL LACTYLIC ACID 7% IN M.O.
▽ GML 12%/LAUROYL LACTYLIC ACID 7% IN M.O.

FIG. 5

4 / 5



- FORMULATION 1
- CONTROL WITHOUT ADHESIVE
- ▽ FORMULATION 4
- ▼ FORMULATION 6
- FORMULATION 8
- FORMULATION 10
- △ FORMULATION 12

N=7 (4 SKIN DONORS)

FIG. 6a

5 / 5

FORMULATION 1

LAUROYL LACTIC ACID	20%
GML	20%
EVA40%va	50%
TESTOSTERONE	10%

FORMULATION 4

CAPROYL LACTIC ACID	20%
L-DEA	20%
EVA40%va	50%
TESTOSTERONE	10%

FORMULATION 6

LAURYL LACTATE	12%
LACTIC ACID	3%
GML	20%
EVA40%va	55%
TESTOSTERONE	10%

FORMULATION 8

LAURYL LACTATE	12%
LACTIC ACID	3%
L-DEA	20%
EVA40%va	55%
TESTOSTERONE	10%

FORMULATION 10

LAUROYL LACTIC ACID	20%
M-DEA	20%
EVA40%va	50%
TESTOSTERONE	10%

FORMULATION 12

LAUROYL LACTIC	12%
LACTIC ACID	3%
M-DEA	20%
EVA40%va	55%
TESTOSTERONE	10%

CONTROL

EVA40%va	98%
TESTOSTERONE	2%

FIG. 6b

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 96/06868A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/14 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 344 651 (SCHWEN R. J. ET AL) 6 September 1994 see column 5, line 18 - line 22 see column 12; examples 4,6 ---	1
X	WO,A,88 06880 (R.I.T.A. CORPORATION) 22 September 1988 see page 6, line 1 - line 9 see page 7, line 1 - line 11 see page 5, line 1 - line 11 ---	1
X	US,A,5 124 354 (GREEN M. R.) 23 June 1992 cited in the application see column 16, line 5 - line 7 see column 16, line 23 --- -/-	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *-&* document member of the same patent family

Date of the actual completion of the international search

2 September 1996

Date of mailing of the international search report

13. 09. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax (+31-70) 340-3016

Authorized officer

Boulois, D

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 96/06868

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 05153 (UNILEVER PLC) 23 February 1995 see page 5, line 23 - line 25 ---	1
A	WO,A,95 09006 (ALZA CORPORATION) 6 April 1995 see claims 1,12,14,16,17 -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 06868

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18-26 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/06868

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DE-T- 3882848	13-01-94
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		JP-B- 7068148	26-07-95
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		EP-A- 0403238	19-12-90
		JP-A- 3063213	19-03-91
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		CA-A- 2166469	23-02-95
		WO-A- 9505160	23-02-95
		EP-A- 0713385	29-05-96
		ZA-A- 9406128	17-07-95
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		CA-A- 2167526	06-04-95
		EP-A- 0721348	17-07-96
		EP-A- 0721349	17-07-96
		WO-A- 9509007	06-04-95
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